specificities, at least one antigen-binding site being specific for VEGF receptor, KDR and the other for FLT-1, and at least one of the antigen binding is specific for a cell surface receptor or a cytokine receptor.

II. (Claims 1-3, 5, 7-24, 26, 28, 37, 39-48, 50-52 and 55-62.) An antigen-binding protein comprising two antigen-binding sites of different specificities, at least one antigen-binding site being specific for VEGF receptor, KDR and the other for FLT-4, and at least one of the antigen binding is specific for a cell surface receptor or a cytokine receptor.

III. (Claims 1-3, 5, 7-24, 26, 29, 33, 37, 39-48, 50-52 and 55-62.) An antigen-binding protein comprising two antigen-binding sites of different specificities, at least one antigen-binding site being specific for VEGF receptor, KDR and the other for EGF-R, and at least one of the antigen binding is specific for a cell surface receptor or a cytokine receptor.

IV. (Claims 1-3, 5, 7-24, 26, 30, 33, 37, 39-48, 50-52 and 55-62.) An antigen-binding protein comprising two antigen-binding sites of different specificities, at least one antigen-binding site being specific for VEGF receptor, KDR and the other for HER-2, and at least one of the antigen binding is specific for a cell surface receptor or a cytokine receptor.

V. (Claims 1-3, 5, 7-24, 26, 31, 33, 37, 39-48, 50-52 and 55-62.) An antigen-binding protein comprising two antigen-binding sites of different specificities, at least one antigen-binding site being specific for VEGF receptor, KDR and the other for FGF-R, and at least one of the antigen binding is specific for a cell surface receptor or a cytokine receptor.

VI. (Claims 1-3, 5, 7-24, 26, 32-33, 37, 39-48, 50-52 and 55-62.) An antigen-binding protein comprising two antigen-binding sites of different specificities, at least one antigen-binding site being specific for VEGF receptor, KDR and the other for PDGR-R, and at least one of the antigen binding is specific for a cell surface receptor or a cytokine receptor.

VII. (Claims 1-3, 5, 7-24, 26, 34, 37, 39-48, 50-52 and 55-62.) An antigen-binding protein comprising two antigen-binding sites of different specificities, at least one antigen-binding site being specific for VEGF receptor, KDR and the other for Tek, and at least one of the antigen binding is specific for a cell surface receptor or a cytokine receptor.

VIII. (Claims 1-3, 5, 7-24, 26, 35, 37, 39-48, 50-52 and 55-62.) An antigen-binding protein comprising two antigen-binding sites of different specificities, at least one antigen-binding site being specific for VEGF receptor, KDR and the other for Tie, and at least one of the antigen binding is specific for a cell surface receptor or a cytokine receptor.

IX. (Claims 1-3, 5, 7-21, 29-30, 38, 39-48, 50-52 and 55-62.) An antigen-binding protein comprising two antigen-binding sites of different specificities, at least one antigen-binding site being specific for EGF-R and the other for HER-2, and at least one of the antigen binding is specific for a cell surface receptor or a cytokine receptor.

X. (Claims 1-2, 4, 6, 7-25, 27, 39-47, 49, 53-54 and 55-62.) An antigen-binding protein comprising two antigen-binding sites of same specificities, at least one antigen-binding site being specific for VEGF receptor, FLT-1, and at least one of the antigen binding is specific for a cell surface receptor or a cytokine receptor.

XI. (Claims 1-2, 4, 6, 7-25, 39-47, 49, and 55-62.) An antigen-binding protein comprising two antigen-binding sites of same specificities, at least one antigen-binding site being specific for VEGF receptor, FLK-1, and at least one of the antigen binding is specific for a cell surface receptor or a cytokine receptor.

XII. (Claims 1-2, 4, 6, 7-24, 26, 39-47, 49-52, and 55-62.) An antigen-binding protein comprising two antigen-binding sites of same specificities, at least one antigen-binding site being specific for VEGF receptor, KDR, and at least one of the antigen binding is specific for a cell surface receptor or a cytokine receptor.

XIII. (Claims 1-2, 4, 6, 7-24, 28, 39-47, 49, and 55-62.) An antigen-binding protein comprising two antigen-binding sites of same specificities, at least one antigen-binding site being specific for VEGF receptor, FLT-4, and at least one of the antigen binding is specific for a cell surface receptor or a cytokine receptor.

XIV. (Claims 1-2, 4, 6, 7-21, 29, 33, 39-47, 49, and 55-62.) An antigen-binding protein comprising two antigen-binding sites of same specificities, at least one antigen-binding site being specific for EGF-R, and at least one of the antigen binding is specific for a cell surface receptor or a cytokine receptor.

XV. (Claims 1-2, 4, 6, 7-21, 30, 33, 39-47, 49, and 55-62.) An antigen-binding protein comprising two antigen-binding sites of same specificities, at least one antigen-binding site being specific for tyrosine kinase receptor, HER-2, and at least one of the antigen binding is specific for a cell surface receptor or a cytokine receptor.

XVI. (Claims 1-2, 4, 6, 7-21, 31, 33, 39-47, 49, and 55-62.) An antigen-binding protein comprising two antigen-binding sites of same specificities, at least one antigen-binding site being specific for FGF-R, and at least one of the antigen binding is specific for a cell surface receptor or a cytokine receptor.

XVII. (Claims 1-2, 4, 6, 7-21, 32, 33, 39-47, 49, and 55-62.) An antigen-binding protein comprising two antigen-binding sites of same

specificities, at least one antigen-binding site being specific for PDGF-R, and at least one of the antigen binding is specific for a cell surface receptor or a cytokine receptor.

XVIII. (Claims 1-2, 4, 6, 7-21, 33-34, 39-47, 49, and 55-62.) An antigen-binding protein comprising two antigen-binding sites of same specificities, at least one antigen-binding site being specific for Tek, and at least one of the antigen binding is specific for a cell surface receptor or a cytokine receptor.

XIX. (Claims 1-2, 4, 6, 7-21, 35, 39-47, 49, and 55-62.) An antigen-binding protein comprising two antigen-binding sites of same specificities, at least one antigen-binding site being specific for Tie-2, and at least one of the antigen binding is specific for a cell surface receptor or a cytokine receptor.

XX. (Claims 64-68.) A method for making a specific antigen-binding protein comprising two antigen-binding sites of different specificities, at least one antigen-binding site being specific for VEGF receptor, KDR and the other for FLT-1, and at least one of the antigen binding is specific for a cell surface receptor or a cytokine receptor.

XXI. (Claims 64-68.) A method for making a specific antigen-binding protein comprising two antigen-binding sites of different specificities, at least one antigen-binding site being specific for VEGF receptor, KDR and the other for FLT-4, and at least one of the antigen binding is specific for a cell surface receptor or a cytokine receptor.

XXII. (Claims 64-68.) A method for making a specific antigen-binding protein comprising two antigen-binding sites of different specificities, at least one antigen-binding site being specific for VEGF receptor, KDR and the other for EGF-R, and at least one of the antigen binding is specific for a cell surface receptor or a cytokine receptor.

XXIII. (Claims 64-68.) A method for making a specific antigen-binding protein comprising two antigen-binding sites of different specificities, at least one antigen-binding site being specific for VEGF receptor, KDR and the other for HER-2, and at least one of the antigen binding is specific for a cell surface receptor or a cytokine receptor.

XXIV. (Claims 64-68.) A method for making a specific antigen-binding protein comprising two antigen-binding sites of different specificities, at least one antigen-binding site being specific for VEGF receptor, KDR and the other for FGF-R, and at least one of the antigen binding is specific for a cell surface receptor or a cytokine receptor.

XXV. (Claims 64-68.) A method for making a specific antigen-binding protein comprising two antigen-binding sites of different specificities, at least one antigen-binding site being specific for VEGF receptor,

KDR and the other for PDF-R, and at least one of the antigen binding is specific for a cell surface receptor or a cytokine receptor.

XXVI. (Claims 64-68.) A method for making a specific antigen-binding protein comprising two antigen-binding sites of different specificities, at least one antigen-binding site being specific for VEGF receptor, KDR and the other for Tek, and at least one of the antigen binding is specific for a cell surface receptor or a cytokine receptor.

XXVII. (Claims 64-68.) A method for making a specific antigen-binding protein comprising two antigen-binding sites of different specificities, at least one antigen-binding site being specific for VEGF receptor, KDR and the other for Tie, and at least one of the antigen binding is specific for a cell surface receptor or a cytokine receptor.

XXVIII. (Claims 64-68.) A method for making a specific antigen-binding protein comprising two antigen-binding sites of different specificities, at least one antigen-binding site being specific for EGF-R and the other for HER-2, and at least one of the antigen binding is specific for a cell surface receptor or a cytokine receptor.

XXIX. (Claims 64-68.) A method for making a specific antigen-binding protein comprising two antigen-binding sites of same specificities, at least one antigen-binding site being specific for VEGF receptor, FLT-1, and at least one of the antigen binding is specific for a cell surface receptor or a cytokine receptor.

XXX. (Claims 64-68.) A method for making a specific antigen-binding protein comprising two antigen-binding sites of same specificities, at least one antigen-binding site being specific for VEGF receptor, FLK-1, and at least one of the antigen binding is specific for a cell surface receptor or a cytokine receptor.

XXXI. (Claims 64-68.) A method for making a specific antigen-binding protein comprising two antigen-binding sites of same specificities, at least one antigen-binding site being specific for VEGF receptor, KDR, and at least one of the antigen binding is specific for a cell surface receptor or a cytokine receptor.

XXXII. (Claims 64-68.) A method for making a specific antigen-binding protein comprising two antigen-binding sites of same specificities, at least one antigen-binding site being specific for VEGF receptor, FLT-4, and at least one of the antigen binding is specific for a cell surface receptor or a cytokine receptor.

XXXIII. (Claims 64-68.) A method for making a specific antigen-binding protein comprising two antigen-binding sites of same specificities, at least one antigen-binding site being specific for EGF-R, and at least one of the antigen binding is specific for a cell surface receptor or a cytokine receptor.

XXXIV. (Claims 64-68.) A method for making a specific antigen-binding protein comprising two antigen-binding sites of same specificities, at least one antigen-binding site being specific for HER-2, and at least one of the antigen binding is specific for a cell surface receptor or a cytokine receptor.

XXXV. (Claims 64-68.) A method for making a specific antigen-binding protein comprising two antigen-binding sites of same specificities, at least one antigen-binding site being specific for FGF-R, and at least one of the antigen binding is specific for a cell surface receptor or a cytokine receptor.

XXXVI. (Claims 64-68.) A method for making a specific antigen-binding protein comprising two antigen-binding sites of same specificities, at least one antigen-binding site being specific for PDGF-R, and at least one of the antigen binding is specific for a cell surface receptor or a cytokine receptor.

XXXVII. (Claims 64-68.) A method for making a specific antigen-binding protein comprising two antigen-binding sites of same specificities, at least one antigen-binding site being specific for Tek, and at least one of the antigen binding is specific for a cell surface receptor or a cytokine receptor.

XXXVIII. (Claims 64-68.) A method for making a specific antigen-binding protein comprising two antigen-binding sites of same specificities, at least one antigen-binding site being specific for Tie-2, and at least one of the antigen binding is specific for a cell surface receptor or a cytokine receptor.

XXXIX. (Claims 69-71.) A method of neutralizing the activation of VEGF-R which comprises treating a cell with an antigen-binding protein wherein at least one of the antigen-binding site is specific for KDR and at least one of the antigen-binding site is specific for FLT-1

XL. (Claims 72-74.) A method of reducing tumor growth which comprises treating a cell with an antigen-binding protein wherein at least one of the antigen-binding site is specific for KDR and at least one of the antigen-binding site is specific for FLT-1

XLI. (Claims 75-77.) A method of inhibiting angiogenesis which comprises treating a cell with an antigen-binding protein wherein at least one of the antigen-binding site is specific for KDR and at least one of the antigen-binding site is specific for FLT-1

Applicants elect, with traverse, to prosecute the invention of Group III, claims 1-3, 5, 7-24, 26, 29, 33, 37, 39-48, 50-52 and 55-62, which are drawn to an antigen-binding protein comprising two antigen-binding sites of different specificity, at least one antigen-binding site being specific for the VEGF receptor KDR and the other for EGFR and at

least one of the antigen binding sites is specific for a cell surface receptor or a cytokine receptor. Applicants reserve the right to file a divisional application directed to the non-elected subject matter.

The present application is directed to a bispecific antigen-binding polypeptide that can exhibit properties of immunoglobulins, (*see* Specification p. 1, ll. 9-10), the process for making the polypeptide of the claimed invention, and uses for the claimed polypeptide. The antigen-binding polypeptide of the claimed invention is uniquely designed to comprise four antigen-binding sites on an IgG-like molecule as opposed to two binding sites on a natural IgG molecule. The antigen-binding sites (a total of four) are preferably located at the N-terminus on one of each of the two light chains and one on each of the two heavy chains, as is shown in Figure 1, bottom left, Bs(scFv)$_4$-Ig. These four antigen-binding sites are optimized to bind to <u>any antigenic epitope</u> of a receptor/cell surface protein, such that the function of receptor/cell surface protein is inactivated upon administration of the antigen-binding polypeptide to a patient. In addition, the antigen-binding polypeptide also maintains the ability of the immunoglobulin-like molecule to activate complement mediated cytotoxicity and antibody dependent cellular toxicity (*see* Specification, p. 1, ll. 13-19; p. 16, ll. 27-28 and Abstract p, p. 49, ll. 1-5).

A key feature of the engineered antigen-binding polypeptide of the present invention is its ability to bind simultaneously, and with increased avidity, to either a single epitope as a result of four available binding sites, or to two or more epitopes from two or more different cell surface antigens to effect a response(s) to the antigen(s) of interest and ultimately to inhibit or disrupt angiogenesis and/or oncogenesis. Exemplary antigen-binding sites for the claimed invention include epitopes derived from the tyrosine kinase family of receptors, such as VEGF receptors (KDR, Flk-1, and Flt-1), FGF-R, PDGF-R, EGF-R, Her-2, Tie-1 and Tek-2, all of which function to regulate angiogenesis and/or oncogenesis (*see* Specification p. 16, ll. 29-32 and p. 17, ll. 1-11). Other examples of epitopes that can be selected to be recognized and bound by the antigen-binding site of the claimed invention are the surface antigens of the immune system effector cells, such as the cytokine and lymphokine receptors Fc receptors and CD molecules (*see* Specification p. 17, ll. 12-30).

The Office sets forth a forty-one-way restriction requirement. Applicants respectfully submit that the restriction is improper, in whole or in part, for the reasons set forth herein and, therefore, request modification or withdrawal.

Applicants submit that the claims of Groups I-XLI are properly presented in a single invention. There are two separate criteria that must be satisfied to support a proper restriction requirement: the invention must be independent or distinct as claimed and there must be a serious burden on the examiner if restriction is required (*See* MPEP §§ 802-03, 806, 808). The Office has shown neither independence or distinctness of the subject matter of the pending claims nor a serious burden without restriction. Accordingly, restriction is improper and the requirement should be withdrawn.

Alternatively, applicants submit that restriction should be imposed only between product and method claims. Therefore, the restriction requirement should be modified as follows:

Group I	(Claims 1-63.) An antigen-binding protein comprising a complex of two first polypeptides and two second polypeptides, the antigen-binding site of the first polypeptide covalently linked to immunoglobulin light chain constant domain (C_L) and the antigen-binding site of the second polypeptide covalently linked to the immunoglobulin heavy chain constant domain (C_H), wherein the antigen-binding sites of the first and second polypeptide can be of the same specificity or a combination of different specificities.
Group II	(Claims 64-77.) A method for making and use of the above antigen-binding protein.

As an additional alternative, applicants respectfully submit that claims 1 and 47 are linking claims and should be treated accordingly. There are a number of situations where one or more claims are inseparable (linking claims) between divisible inventions. Common types of linking claims include genus claims linking species claims and claims to a product linking a process of making and a process of using. *See* MPEP § 809. Claims 1 and 47 are directed to the product of the claimed invention, namely the antigen-binding polypeptide with a structure comprising four antigen-binding sites, which may be derived from single chain Fv, each covalently linked to the immunoglobulin light and heavy chain constant domains. Claim 64 is a directed to a process of making the product of claims 1 and 47. Claims 69, 72 and 75 are directed to use of the product of claims 1 and 47.

Accordingly, claims 1 and 47 are independently inseparable from the remainder of the claims and should be treated as a linking claim.

II. CONCLUSION

In view of the foregoing remarks, Applicants respectfully request the Examiner to reconsider the requirement for restriction. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

The Office is authorized to charge any required fees that may be necessary for consideration of this paper to Kenyon & Kenyon Deposit Account No. 11-0600.

Respectfully submitted,

Kathryn M. Lumb, Reg. No. 46,885
KENYON & KENYON
One Broadway
New York, NY 10004
(212) 908-6277 (telephone)
(212) 425-5288 (facsimile)

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